

WHAT IS CLAIMED IS:

1. A method of treating pain, inflammation or an inflammation mediated disorder, the method comprising:

(a) diagnosing a subject in need of treatment for pain, inflammation or an inflammation mediated disorder; and

5 (b) administering to the subject a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof and a calcium modulating agent or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

2. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC<sub>50</sub> to COX-2 IC<sub>50</sub> not less than about 50.

3. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC<sub>50</sub> to COX-2 IC<sub>50</sub> not less than about 100.

4. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, meloxicam, parecoxib, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide, 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid, (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone, and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

5. The method of claim 1 wherein the calcium modulating agent is selected from the group consisting of nimodipine, nicardipine, nifedipine, amolodipine, isradipine, diltiazem, verapamil, bepridil, gallopamil, flunarizine, and pimozide.

6. The method of claim 4 wherein the calcium modulating agent is selected from the group consisting of nimodipine, nicardipine, nifedipine, amolodipine, isradipine, diltiazem, verapamil, bepridil, gallopamil, flunarizine, and pimozide.

7. A method of treating pain, inflammation or an inflammation mediated disorder, the method comprising:

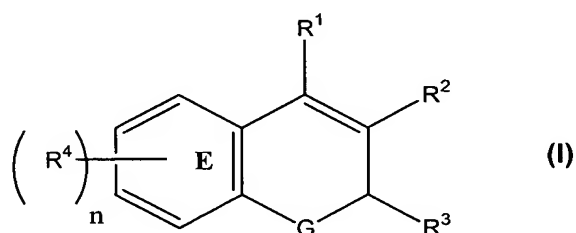
(a) diagnosing a subject in need of treatment for pain, inflammation or an inflammation mediated disorder; and

5 (b) administering to the subject a calcium modulating agent or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof and a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein the cyclooxygenase-2 selective inhibitor is a chromene compound, the chromene compound comprising a benzothiopyran, a  
10 dihydroquinoline or a dihydronaphthalene.

8. The method of claim 7 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC<sub>50</sub> to COX-2 IC<sub>50</sub> not less than about 50.

9. The method of claim 7 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC<sub>50</sub> to COX-2 IC<sub>50</sub> not less than about 100.

10. The method of claim 7 wherein the cyclooxygenase-2 selective inhibitor is a compound having the formula



wherein:

n is an integer which is 0, 1, 2, 3 or 4;

5 G is O, S or NR<sup>a</sup>;

R<sup>a</sup> is alkyl;

R<sup>1</sup> is selected from the group consisting of H and aryl;

R<sup>2</sup> is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

10  $R^3$  is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

each  $R^4$  is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or  $R^4$  together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

11. The method of claim 7 wherein the cyclooxygenase-2 selective inhibitor is (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

12. The method of claim 7 wherein the calcium modulating agent is selected from the group consisting of nimodipine, nicardipine, nifedipine, amolodipine, isradipine, diltiazem, verapamil, bepridil, gallopamil, flunarizine, and pimozone.

13. A method of treating pain, inflammation or an inflammation mediated disorder, the method comprising:

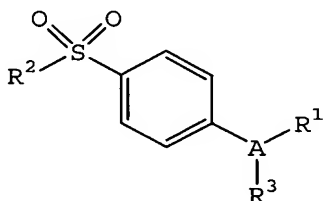
(a) diagnosing a subject in need of treatment for pain, inflammation or an inflammation mediated disorder; and

5 (b) administering to the subject a calcium modulating agent or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof and a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein the cyclooxygenase-2 selective inhibitor is a tricyclic compound, the tricyclic compound comprising a benzenesulfonamide or  
10 methylsulfonylbenzene.

14. The method of claim 13 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1  $IC_{50}$  to COX-2  $IC_{50}$  not less than about 50.

15. The method of claim 13 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC<sub>50</sub> to COX-2 IC<sub>50</sub> not less than about 100.

16. The method of claim 13 wherein the cyclooxygenase-2 selective inhibitor is a compound of the formula:



wherein:

A is selected from the group consisting of partially unsaturated or  
5 unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R<sub>1</sub> is selected from the group consisting of heterocyclyl, cycloalkyl,  
cycloalkenyl and aryl, wherein R<sup>1</sup> is optionally substituted at a substitutable position  
with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl,  
alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino,  
10 nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R<sub>2</sub> is selected from the group consisting of methyl and amino; and

R<sub>3</sub> is selected from the group consisting of H, halo, alkyl, alkenyl,  
alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycliloxy, alkyloxy, alkylthio,  
alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl,  
15 heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxyalkyl, arylcarbonyl,  
aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl,  
aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxyalkylalkyl, aminocarbonyl,  
aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-  
arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-aryl amino,  
20 N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-aryl amino, aminoalkyl,  
alkylaminoalkyl, N-aryl aminoalkyl, N-aralkyl aminoalkyl, N-alkyl-N-aralkyl aminoalkyl,  
N-alkyl-N-aryl aminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl,  
alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl,  
and N-alkyl-N-arylaminosulfonyl.

17. The method of claim 13 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, valdecoxib, parecoxib, deracoxib, rofecoxib, etoricoxib, and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

18. The method of claim 13 wherein the calcium modulating agent is selected from the group consisting of nimodipine, nicardipine, nifedipine, amlodipine, isradipine, diltiazem, verapamil, bepridil, gallopamil, flunarizine, and pimozide.

19. A method of treating pain, inflammation or an inflammation mediated disorder, the method comprising:

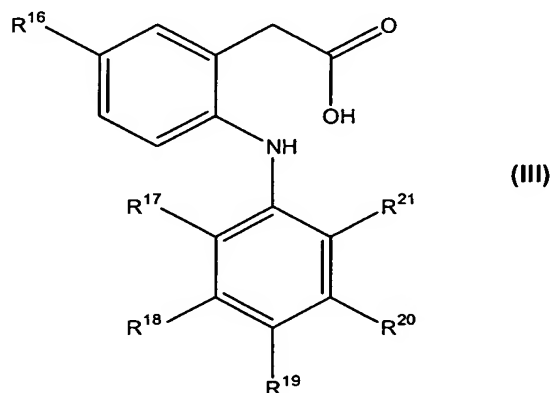
(a) diagnosing a subject in need of treatment for pain, inflammation or an inflammation mediated disorder; and

5 (b) administering to the subject a calcium modulating agent or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof and a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein the cyclooxygenase-2 selective inhibitor is a phenyl acetic acid compound.

20. The method of claim 19 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1  $IC_{50}$  to COX-2  $IC_{50}$  not less than about 50.

21. The method of claim 19 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1  $IC_{50}$  to COX-2  $IC_{50}$  not less than about 100.

22. The method of claim 19 wherein the cyclooxygenase-2 selective inhibitor is a compound having the formula:



wherein:

R<sub>16</sub> is methyl or ethyl;

5 R<sub>17</sub> is chloro or fluoro;

R<sub>18</sub> is hydrogen or fluoro;

R<sub>19</sub> is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or  
hydroxy;

R<sub>20</sub> is hydrogen or fluoro; and

10 R<sub>21</sub> is chloro, fluoro, trifluoromethyl or methyl; and

provided that each of R<sub>17</sub>, R<sub>18</sub>, R<sub>19</sub> and R<sub>20</sub> is not fluoro when R<sub>16</sub> is  
ethyl and R<sub>19</sub> is H.

23. The method of claim 22

wherein:

R<sub>16</sub> is ethyl;

R<sub>17</sub> and R<sub>19</sub> are chloro;

5 R<sub>18</sub> and R<sub>20</sub> are hydrogen; and

R<sub>21</sub> is methyl.

24. The method of claim 19 wherein the calcium modulating agent is  
selected from the group consisting of nimodipine, nicardipine, nifedipine,  
amlodipine, isradipine, diltiazem, verapamil, bepridil, gallopamil, flunarizine, and  
pimozide.

25. A method of treating pain, inflammation or an inflammation mediated  
disorder, the method comprising:

(a) diagnosing a subject in need of treatment for pain, inflammation  
or an inflammation mediated disorder; and

5 (b) administering to the subject a cyclooxygenase-2 selective  
inhibitor selected from the group consisting of celecoxib, deracoxib, valdecoxib,  
rofecoxib, lumiracoxib, etoricoxib, parecoxib, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-

methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid; and

10           a calcium modulating agent selected from the group consisting of nimodipine, nicardipine, nifedipine, amolodipine, isradipine, diltiazem, verapamil, bepridil, gallopamil, flunarizine, and pimozide.

26.    The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is celecoxib.

27.    The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is deracoxib.

28.    The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is valdecoxib.

29.    The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is rofecoxib.

30.    The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is etoricoxib.

31.    The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is parecoxib.

32.    The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

33.    The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

34.    The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is lumiracoxib.

35.    The method of claim 1 wherein the inflammation mediated disorder is arthritis.

36.    The method of claim 1 wherein the inflammation mediated disorder is a gastrointestinal disorder.

37. The method of claim 36 wherein the gastrointestinal disorder is selected from the group consisting of inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis.